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Ambient Water Quality Criteria Document
Addendum for Haloethers

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ADDENDUM FOR HALOETHERS

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Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority Pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five years. These addenda represent an updated literature search current as of 1988, plus additional information from Agency files and Program Offices. This addendum is to update the existing Ambient Water Quality Criteria Document for Haloethers.

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PREFACE

Under the 1977 Clean Water Act, Congress mandated the U.S. Environmental Protection Agency to develop ambient water quality criteria for 129 priority pollutants. These criteria were published in 1980. Under Section 304(a)(1) of the Clean Water Act as amended in 1987, the U.S. EPA is mandated to re-evaluate and update these criteria every five years. These addenda represent an updated literature search current as of 1988, plus additional information from Agency files and Program Offices. The first draft of this addendum was prepared by Syracuse Research Corporation under contract no. 68-C8-0004.

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
CRAVE	Carcinogen Risk Assessment Verification Endeavor
EPN	O-ethyl O-p-nitrophenyl phenylphosphonothioate
LOAEL	Lowest-observed-adverse-effect level
MFO	Mixed function oxidase
NOAEL	No-observed-adverse-effect level
RFD	Reference dose

INTRODUCTION

Under Section 304(a)(1) of the Clean Water Act of 1977 as amended in 1987, the U.S. EPA is required to publish criteria for water quality accurately reflecting the latest scientific knowledge regarding the effects on health and welfare that may occur from the presence of pollutants in any body of water, including groundwater. In accordance with the 1977 act, Ambient Water Quality Criteria Documents (AWQCDs) were developed in 1980 for 65 toxic pollutants or classes of pollutants listed under Section 307(a)(1).

These addenda are intended to serve as an update of the original AWQCDs. The addenda provide the Agency with the latest scientific assessments of potential health hazards associated with these pollutants and serve as guidelines for modifying the current (1980) AWQCDs.

The human health criteria in these addenda are based on Agency verified risk assessment values when available. These values consist of reference doses (RfD) for those chemicals believed to be systemic toxicants (i.e., do not induce cancer) and cancer risk factors for those thought likely to cause cancer in humans. The verification process consists of a review and consensus of risk assessment values provided by an Agency workgroup consisting of scientists from each of the major Agency offices. Assessments for noncarcinogens are verified by the RfD workgroup and those for carcinogens are verified by the Carcinogen Risk Assessment Verification Endeavor (CRAVE) workgroup. If such values are not available, the criteria are based on the most recent Agency health assessment. In the absence of any appropriate Agency value, RfD values or cancer risk factors are derived by current Agency methods if adequate new data are available, and criteria are recommended based on the proposed RfD or risk factor.

The RFD is an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RFD is derived by dividing a NOAEL or LOAEL for subchronic or chronic exposure by standard uncertainty factor(s) times an additional uncertainty factor:

$$RFD = \frac{NOAEL \text{ or } LOAEL}{UF(s) \times UF}$$

The standard uncertainty factors are applied to reflect the various types of data used to estimate RfDs. An uncertainty factor of 10 is used to account for variations in human sensitivity when extrapolating from valid human studies involving long-term exposure of average, healthy subjects. An additional 10-fold factor is used for each of the following: to extrapolate from long-term animal studies to the case of humans, to extrapolate from subchronic animal studies to chronic exposure, and to extrapolate from a LOAEL to a NOAEL. An additional uncertainty factor of >0-10 may be applied to reflect professional assessment of the uncertainties of the study and data base not explicitly addressed by the standard uncertainty factors (i.e., completeness of the overall data base). The default value for the additional uncertainty factor is 1.

In assessing the carcinogenic potential of a chemical, the U.S. EPA classifies the chemical into one of the following groups according to the degree of evidence in epidemiological studies and animal studies: Group A - Human Carcinogen; Group B - Probable Human Carcinogen [limited evidence in humans with or without sufficient evidence in animals (Group B1) or inadequate evidence in humans with sufficient evidence in animals (Group B2)]; Group C - Possible Human Carcinogen (limited evidence of carcinogenicity in animals in the absence of human data); Group D - Not Classifiable as to

Human Carcinogenicity (Inadequate or no evidence); Group E - Evidence of Noncarcinogenicity for Humans. Quantitative carcinogenic risk assessments are performed for chemicals in Groups A and B, and on a case-by-case basis for chemicals in Group C. Upper-bound cancer unit risks (slope values) are estimated through the use of mathematical extrapolation models. Most commonly for animal data, the linearized multistage model with a 95% upper confidence limit is used to provide a low-dose estimate of cancer risk. The cancer risk is characterized as an upper-limit estimate (i.e., the true risk to humans, while not identifiable, is not likely to exceed the upper-limit estimate and in fact may be lower). Alternative risk models to the multistage model, such as the one-hit, Weibull, Logit or Probit model, are available and may be used when the evidence indicates that they may be more appropriate. In the absence of such evidence, the Agency recommends the linearized multistage model to provide consistency of approach and an upper-bound on the potential carcinogenic risk. In the case where human data are used for quantitative risk assessment, an upper-bound estimate rather than a 95% upper-bound estimate is used when low-dose linearity is assumed.

In the development of this Addendum to the AWQCD on haloethers, recent Agency assessments have been consulted. A computerized literature search was conducted to cover studies published more recently than the latest Agency assessment (i.e., published in 1987 to 1988). New key studies have been evaluated.

REVIEW OF NEW DATA

This document reviews halogenated aromatic ethers including chlorophenyl phenyl ethers (chlorodiphenyl ethers), bromophenyl phenyl ethers (bromodiphenyl ethers) and polychlorinated diphenyl ethers in the original AWQCD. Chloroalkyl ethers are discussed in a separate document.

Recent Agency evaluations of the toxicity of halogenated aromatic ethers, which included a HEEP on 4-bromophenyl phenyl ether (U.S. EPA, 1986) and a HEED on haloethers (U.S. EPA, 1987), have failed to identify toxicity data appropriate for estimation of RfDs or cancer potency factors for any of the aromatic ethers that are the subject of this document. Data identified for this addendum are limited to a pharmacokinetic study and two acute studies.

Toxicologic/Carcinogenic Effects

Chui et al. (1987) investigated the fate of 4-chlorodiphenyl ether in male Sprague-Dawley rats. Unchanged ^{14}C -4-chlorodiphenyl ether was not detected in the blood 2 hours after intravenous administration of an 850 nmol/kg dose. Total radioactivity was excreted slowly, with ~41 and 33% of the dose excreted in the urine and feces, respectively, in 1 week. In the urine, >90% of the radioactivity was identified as the 4'-hydroxy derivative of 4-chlorodiphenyl ether. The investigators proposed a metabolic pathway involving arene oxide formation with the production of intermediates that bind irreversibly to macromolecules. In vitro studies demonstrated that metabolites of 4-chlorodiphenyl ether bound irreversibly with rat liver microsomal protein.

Investigations by Chui et al. (1985) and Carlson et al. (1980) demonstrated that the chlorodiphenyl ethers induce MFO, aryl hydrocarbon hydroxylase and EPN detoxification activities when administered by gavage or

intraperitoneal injection to male Sprague-Dawley rats. Some chlorodiphenyl ethers behaved similarly to phenobarbital-type inducers and some behaved similarly to mixed-type or methylcholanthrene-type inducers, with the nature of the induction dependent upon number and position of chlorine substituents. Carlson et al. (1980) reported that the chlorodiphenyl ethers were generally less active inducing agents than brominated diphenyl ethers.

U.S. EPA (1986) discussed a negative pulmonary adenoma assay in strain A mice given intraperitoneal injections of 4-bromodiphenyl ether (Theiss et al., 1977). No cancer data were located for any of the other halogenated diphenyl ethers. U.S. EPA (1986) classified 4-bromodiphenyl ether in the U.S. EPA Group D, not classifiable as to human carcinogenicity. Also, U.S. EPA (1987) stated that the other halogenated aromatic ethers should be assigned to Group D because of the lack of human or animal data.

Bioconcentration Factor (BCF)

Pertinent information concerning the bioconcentration factor for haloethers are currently undergoing Agency review. The appropriate bioconcentration data will be incorporated upon completion of this review.

QUANTIFICATION OF EFFECTS

At the time of preparation of the original AWQCD (U.S. EPA, 1980) and subsequent revision (U.S. EPA, 1982) data were insufficient for derivation of ambient water quality criteria for protection of human health. Newer data suggest that 4-chlorodiphenyl ether is metabolized via arene oxide formation to intermediates that bind covalently to macromolecules (Chui et al., 1987) and that the halogenated aromatic ethers induce hepatic drug-metabolizing enzyme activity (Carlson et al., 1980; Chui et al., 1985). Although these data suggest that the halogenated aromatic ethers may be potent toxicants, data are insufficient for derivation of ambient water quality criteria for any of these compounds.

EXISTING STANDARDS AND CRITERIA

Current data regarding existing standards and criteria for halogenated aromatic ethers were not located in the available literature.

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